

EXHIBIT J

Ma W, Eisenach JC. Cyclooxygenase 2 in infiltrating inflammatory cells in injured nerve is universally up-regulated following various types of peripheral nerve injury. *Neuroscience*. 2003;121(3):691-704.

We previously reported the up-regulation of cyclooxygenase 2 (COX2) in injured sciatic nerve of rats with partial sciatic nerve ligation (PSNL) and the reversal of PSNL-elicited tactile allodynia by local injection of the COX inhibitor ketorolac [Eur J Neurosci 15 (2002) 1037]. We further asked whether COX2 up-regulation in injured nerve is a universal phenomenon following various types of nerve injury. In the current study, we observed that abundant COX2 immunoreactive (IR) cell profiles appeared in injured nerves of rats following spinal nerve ligation (SNL), chronic constriction injury (CCI) and complete sciatic nerve transection. Most COX2-IR cells were identified as infiltrating macrophages. Partial injury induced greater COX2 up-regulation than complete injury. COX2 up-regulation reached a peak at 2-4 weeks, evidently declined by 3 months and disappeared by 7 months postlesion. These findings suggest that up-regulation of COX2 in injured nerve is a common event during the initial several months after nerve injury. We observed that local ketorolac-elicited anti-allodynia was closely associated with the abundance of COX2-IR cells in injured nerve, varying with the type of injury and time after injury. The anti-allodynia lasted the longest when local ketorolac was given 2-4 weeks after PSNL, CCI and SNL. The duration of local ketorolac's anti-allodynia was the longest in CCI rats, which also exhibited the most abundant COX2 up-regulation. Local ketorolac's anti-allodynia lasted much shorter when given 2-3 months after lesion. Local ketorolac failed to induce anti-allodynia 7 months after lesion, a time when COX2-IR cells completely disappeared from the injured nerve except a few cells at the injury site. Our data strongly suggest that during the initial several months after nerve injury, peripherally over-produced prostaglandins play an important role in the maintenance of neuropathic pain.
